Genetic variants of the alpha-synuclein gene SNCA are associated with multiple system atrophy

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Résumé en anglais	Background Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized by parkinsonism, cerebellar ataxia and autonomic dysfunction. Pathogenic mechanisms remain obscure but the neuropathological hallmark is the presence of α-synuclein-immunoreactive glial cytoplasmic inclusions. Genetic variants of the α-synuclein gene, SNCA, are thus strong candidates for genetic association with MSA. One follow-up to a genome-wide association of Parkinson's disease has identified association of a SNP in SNCA with MSA. Methodology/Findings We evaluated 32 SNPs in the SNCA gene in a European population of 239 cases and 617 controls recruited as part of the Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) study. We used 161 independently collected samples for replication. Two SNCA SNPs showed association with MSA: rs3822086 (P = 0.0044), and rs3775444 (P = 0.012), although only the first survived correction for multiple testing. In the MSA-C subgroup the association strengthened despite more than halving the number of cases: rs3822086 P = 0.0024, OR 2.153, (95% CI 1.3–3.6); rs3775444 P = 0.0017, OR 4.386 (95% CI 1.6–11.7). A 7-SNP haplotype incorporating three SNPs either side of rs3822086 strengthened the association with MSA-C further (best haplotype, P = 8.7×10−4). The association with rs3822086 was replicated in the independent samples (P = 0.035). Conclusions/Significance We report a genetic association between MSA and α-synuclein which has replicated in independent samples. The strongest association is with the cerebellar subtype of MSA.
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